Studies on Oxasteroids. I. Synthesis of 3-Cyano-3-methylchroman-4-one.

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Condensation of chroman-4-one with ethyl formate in the presence of sodium methoxide gave 3-hydroxymethylenechroman-4-one (II). Reaction of II with hydroxylamine hydrochloride, followed isomerization by potassium *t*-butoxide gave IV. 3-Cyano-3-methylchroman-4-one was obtained by methylation of IV or treatment of III with potassium *t*-butoxide and methyl iodide.

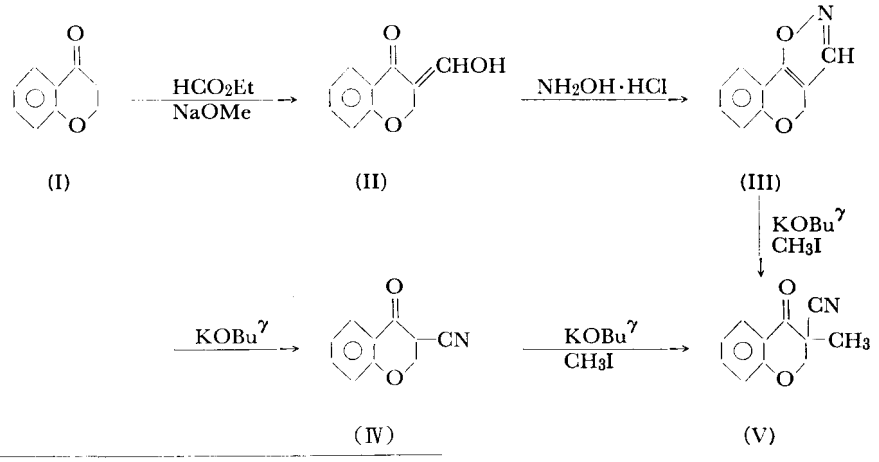
The synthetic modifications of naturally occurring steroids have resulted in the discovery of a number of potent, highly specific, commercially important therapeutic agents. Exception for some examples*), none of these has involved modification of the basic carbon skeleton of the steroid nucleus itself, but during recent decade the syntheses of the oxasteroids are reported by many workers. These are 2-oxa-[1], 3-oxa-[2], 4-oxa-[3], 6-oxa-[4], 7-oxa-[5], 12-oxa-[6], 16-oxa-[7], and 17-oxa-steroid[8].

It is apparent that no steroid analogs has been prepared in which 11-position of steroid nucleus contains oxygen substituted for carbon, and in our laboratory the synthesis of 11-oxasteroid is attempted. The recent publication[9] of Kasturi and Damodaran on the applications of 7-methoxychroman-4-one derivatives in steroid synthesis has prompted us to report the present synthesis of the title compound.

Chroman-4-one, as the starting material in the present studies, was obtained by cyclodehydration of β-phenoxypropionic acid with polyphosphoric acid at 90°[10]. Preliminary attempts to prepare 3-cyanochroman-4-one by replacement of bromine atom of 3-bromochroman-4-one with nitrile group using alkali cyanide under various conditions were so unpromising that the other method, which is applied to the Johnson's method[11], was tried.

Since it has been shown that the methylene group at 3 position in chroman-4-one is more reactive than the methylene group at 2 position and that the Claisen condensation of 1-tetralone with ethyl formate gave 2-hydroxymethylenetetralone-1[12], it is expected that the Claisen condensation with ethyl formate would be similarly carried out in the chroman-4-one series and was shown in Chart 1.

Chart 1



*) These are 19-nor- and 18, 19-bisnor-series.

Chroman-4-one was condensed with ethyl formate in dry benzene in the presence of sodium methoxide to give the corresponding 3-hydroxymethylene derivative (II) in 88.7% yield. The IR spectra [1640 cm^{-1} (C=O)] and microanalyses of II are in agreement with the expected structure.

The interaction of hydroxymethylene II with hydroxylamine hydrochloride in acetic acid gave the isoxazole (III) in 93.1% yield. The IR spectra of III shows bands at 1670 cm^{-1} (C=N).

R. B. Woodward *et at.*[13] reported that the isoxazole was readily isomerized to cyano ketone by cleavage of O-N bond in the presence of basic catalysts. The isomerization of isoxazole III in dry benzene in the presence of potassium *t*-butoxide at room temperature gave 3-cyanochroman-4-one (IV) in yield of 69.2%. The IR spectra have absorption bands of nitrile and carbonyl group at 2200 and 1700 cm^{-1}, respectively. Whereas the isomerization with sodium methoxide in methanol or sodium ethoxide in ethanol gave only unidentified materials.

Methylation of cyanoketone IV with potassium *t*-butoxide and methyl iodide in *t*-butanol gave 3-cyano-3-methylchroman-4-one (V) in yiele of 70.9%. The IR spectra [(nujol) 2200 (C≡N) and 1700 cm^{-1} (C=O)] and microanalyses of V are in agreement with the expected structure. The isomerization of III followed methylation with methyl iodide in the presence of potassium *t*-butoxide gave V in yield of 85.5%, whereas the same treatment with sodium ethoxide gave V in 14.2% yield and the use of sodium methoxide gave no expected product.

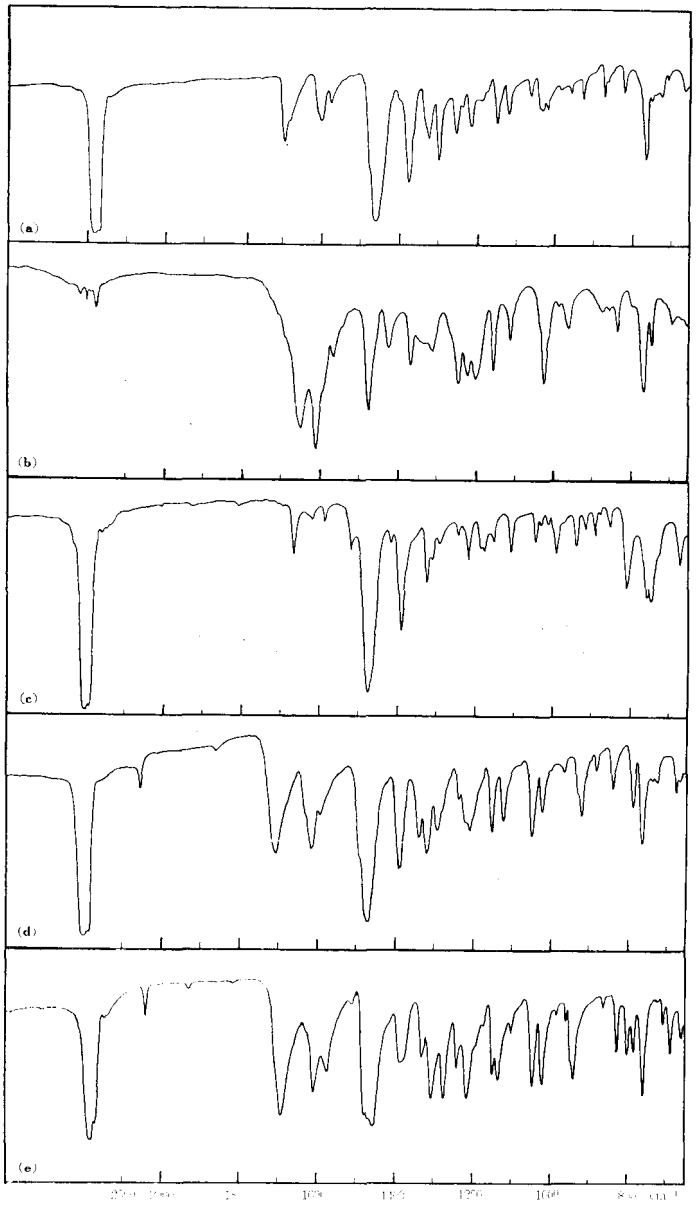


Fig. 1. IR spectra of I (a), II (b), III (c), IV (d), and V (e)

Experimental Section*)

Chroman-4-one (I) was prepared by cyclization of β-phenoxypropionic acid[10] with polyphosphoric acid**). The IR spectra is shown in Fig. 1(a).

The 2, 4-dinitrophenylhydrazone was prepared by

*) All boiling and melting points are uncorrected. Microanalyses were performed by Miss H. Otani and T. Nisi.

**) Polyphosphoric acid was prepared from 320 ml of 85% phosphoric acid and 500 g of phosphorus pentoxide by heating at 180° to obtain homogeneous sloution.

usual method[14] and melted at 239—242° (from ethyl acetate).

Anal. Calcd. for $C_{15}H_{12}N_4O_5$: C, 54.88; H, 3.68; N, 17.07. Found: C, 54.87; H, 3.83; N, 17.14.

3-Hydroxymethylenechroman-4-one (II). — To a suspended solution of 11.4g of sodium methoxide and 15.6g of ethyl formate in 100ml of dry benzene was added a solution of 14.8g of chroman-4-one in 100ml of benzene with cooling and the resulting mixture was stirred for 4 hr at room temperature. A yellow precipitate gradually formed. The mixture was hydrolyzed with 100 ml of water and the organic layer was extracted with 5% sodium hydroxide solution. The alkaline layers were combined, washed with ether, and acidified with cold hydrochloric acid. The separated oil was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and concentrated to give 15.6g (88.7%) of crude product, which was satisfactory for the next step. Distillation of crude product gave a yellow viscous oil, bp 130—140°/5—6 mm, n^{25} 1.6278, accompanying decomposition. The IR spectra is shown in Fig. 1 (b).

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58: Found: C, 67.17; H, 4.70.

Chromano[4,3-d]isoxasole (III). — A solution of 15.3g of crude 3-hydroxymethylenechroman-4-one in 140 ml of acetic acid was stirred for 8 hr at 70—80° with 15.0g of powdered hydroxylamine hydrochloride. The most of acetic acid was removed at reduced pressure, and the residue was diluted with water and extracted with ether. The extract was washed with saturated sodium bicarbonate solution and with water, dried (Na_2SO_4), and concentrated to give 14.0g (93.1%) of crude isoxazole. Recrystallizations from ligroin gave a pure chromano[4,3-d]isoxazole of mp 56—58°. The IR spectra is shown in Fig. 1 (c).

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.08; H, 4.27; N, 8.40.

3-Cyanochroman-4-one (IV). — To a cooled solution of 1.5g of potassium in 45ml of *t*-butanol was added a solution of 2.6g of isoxazole III in 60 ml of benzene. After stirring for 2 hr at room temperature, the mixture was hydrolyzed with water and extracted with 5% sodium hydroxide solution. The combined alkaline extract was acidified with cold hydrochloric acid. The separated oil was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and concentrated to give 2.5g (96.2%) of 3-cyanochroman-4-one.

Recrystallization from ethanol gave a pure sample of mp 86.5—87.5°. The IR spectra is shown in Fig. 1 (d).

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.63; H, 4.09; N, 8.10.

3-Cyano-3-methylchroman-4-one (V). A. Directly from III with potassium *t*-butoxide. — A solution of 2.0g of potassium in 60ml of *t*-butanol was added to a cooled solution of 3.6g of III and 10 ml of methyl iodide in 90 ml of *t*-butanol. After stirring for 5 hr at 40—45°, the solvent was largely removed at reduced pressure. The residue was taken up in a mixture of ether and benzene, washed with dilute sodium hydroxide solution, dilute hydrochloric acid, and with water, dried(Na_2SO_4), and concentrated. The residue was recrystallized from ethanol to give 3.2g (85.8%) of 3-cyano-3-methylchroman-4-one, mp 69—70.5°. The IR spectra is shown in Fig. 1 (e).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.76; H, 5.01; N, 7.65.

The 2,4-dinitrophenylhydrazone melted at 202—204° (from ethyl acetate).

Anal. Calcd. for $C_{17}H_{13}N_5O_5$: C, 55.59; H, 3.57; N, 19.07. Found: C, 55.21; H, 3.83; N, 18.88.

B. Directly from III with sodium ethoxide. — To a cooled solution of 2.7g of III and 8.0 ml of methly iodide in 60 ml of ethanol was added a solution of 1.0g of sodium in 40ml of ethanol with stirring. After stirring for 5 hr at room temperature, the most of the solvent was removed. The residue was diluted with water and extracted with a mixture of ether and benzene. The extract was washed with 5% sodium hydroxide solution, dilute hydrochloric acid and with water, dried (Na_2SO_4), and concentrated to give 0.4g (14.2%) of V.

C. From IV. — To a cooled solution of 1.3g of IV and 6 ml of methyl iodide in 40 ml of *t*-butanol was added a solution of 0.6g of potassium in 30ml of *t*-butanol with stirring. After stirring for 5 hr at 40—50°, the solvent was largely removed at reduced pressure. The residue was diluted with water and taken up

in a mixture of ether and benzene. The extract was washed with 5% sodium hydroxide solution, dilute hydrochloric acid and with water, dried (Na_2SO_4), and concentrated to give 1.0 g (70.9%) of V.

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